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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,882	03/22/2004	Christopher J. Frederickson	D6489	9873

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EXAMINER	
HUYNH, CARLIC K	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,882	FREDERICKSON, CHRISTOPHER J.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *7-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2007 and 27 July 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-34 are pending in the application, with claims 7-34 having been withdrawn from consideration, in response to the restriction requirement submitted on April 30, 2007. Accordingly, claims 1-6 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election without traverse of the claims of Group I, namely claims 1-6, in the reply filed on May 31, 2007 is acknowledged.

Claims 7-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on May 31, 2007.

3. Applicant's election with traverse of the species of (1) an agent that inhibits nitric oxide synthase (nNOS and iNOS) and (2) an agent that increase eNOS activity, in the reply filed on May 31, 2007 is acknowledged. The traversal is on the ground(s) that the methods of the invention rely on the combination of inhibition of nNOS and iNOS as well as activation of eNOS in order to prevent zinc-mediated brain injury.

Applicant's arguments were not found persuasive. Applicant acknowledges that "structurally species 1 and 2 encompass distinct compounds" in the Response to Elected/Restriction filed on May 31, 2007. Furthermore, the claims of group I, claims 1-6, are directed to a method of inhibiting zinc release comprising providing one agent that inhibits nitric

oxide synthesis and does not specifically include an agent to activate eNOS. The agents that inhibit nNOS and iNOS as well as the agents that activate eNOS are structurally distinct and thus would present a search burden for the Examiner.

The election/restriction requirement is deemed proper and is made FINAL.

Information Disclosure Statement

The Information Disclosure Statement has not been submitted at the time of this Office Action.

Drawings

4. The drawings, filed on March 22, 2004 and July 27, 2004, are objected to because the copies are too dark. Specifically, Figures 2A, 4A-F, 6, and 10A-D are too dark and thus prevent their proper interpretation. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet"

or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 5-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a zinc-mediated brain injury by inhibiting zinc-release, does not reasonably provide enablement for preventing a zinc-mediated brain injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method of inhibiting zinc release from neurons, wherein the inhibtion of zinc release prevents a zinc-mediated brain injury.

(2). ***State of the Prior Art***:

The skilled artisan would view that the prevention of a zinc-mediated brain injury, e.g. epilepsy or seizure, is highly unlikely.

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the arts of zinc pharmacology as well as epilepsy and other seizure disorders are extremely high.

(4). ***Predictability of the Art***:

The prevention of a zinc-mediated brain disorder such as epilepsy is highly unpredictable. The prior art does not teach a method to prevent epilepsy. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of inhibiting zinc release from neurons, wherein the inhibtion of zinc release prevents a zinc-mediated brain injury.

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to the method for inhibiting zinc release from neurons, wherein the inhibition of zinc release prevents a zinc-mediated brain injury is limited.

The disclosure of the methods of inhbiting zinc release are adequate (pp. 36-65, examples 2-10).

(7). ***Working Examples***:

The working examples in the specification show the role of nitric oxide on neuronal zinc release (see pp. 36-43, Examples 2-3). However, there are no examples to preventing a zinc-mediated brain injury in the specification. Thus, the working examples show how to treat, not how to prevent.

Note that lack of a working example to prevent, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of a method to prevent zinc-mediated brain injury. As a result, one of skill in the art would be forced to perform an exhaustive search

for the embodiments of any drugs and methods having the function recited in the instant claim suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without ***undue experimentation***.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Montécot et al. (Neuroscience, 1998, Vol. 84, No. 3, pp. 791-800).

Montécot et al. teach that system administration of 7-nitroindazole, a selective inhibitor of neuronal nitric oxide synthase (nNOS), inhibited hippocampal NOS activity and protects neurons from seizure-induced toxicity (abstract).

It is noted that the instant claims entail only the step of administering an agent, e.g. 7-nitroindazole, to inhibit nitric oxide synthase in neurons.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frederickson (International Review of Neurobiology, 1989, Vol. 31, pp. 145-238) in view of Bagetta et al. (Biochemical and Biophysical Research Communications, 2002, Vol. 291, pp. 255-260) and Suh et al. (Brain Research, 2001, Vol. 895, pp. 25-32).

Frederickson defines zinc-containing neurons as neurons that selectively concentrate zinc in their axonal boutons (pp. 196-197). Thus, the zinc is stored in the presynaptic vesicles of the zinc-containing neurons. Frederickson teaches that the mossy fiber axons of the hippocampus are the most thoroughly studied of the zinc-containing fiber systems (p. 197). Frederickson further teaches that zinc plays a role in epilepsy (p. 216). CNS zinc levels are abnormal in the brains of seizure prone laboratory animals and in the brains and body fluids of human patients with seizure related disorders (pp. 216-217). Furthermore, the heaviest concentrations of zinc-containing boutons are in the seizure-prone limbic regions of the brain, e.g. the hippocampus (pp. 216-217).

Frederickson does not teach the involvement of nitric oxide synthase, either nNOS or eNOS, in seizures and chelating zinc to treat seizures.

Bagetta et al. teach enhancement of the expression of neuronal nitric oxide synthase (nNOS) by administration of tacrine triggers limbic seizures and damage to the hippocampus in rats and that pretreatment with 7-nitroindazole, a selective inhibitor of nNOS, prevented the seizures and abolished neuronal cell death in the hippocampus (abstract).

Suh et al. teach that chelatable zinc ions release from zinc-enriched synaptic vesicles are involved in seizure-induced neuronal death in the hippocampus (abstract).

Accordingly, absence the showing of unexpected results, it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy or seizures because the compounds of Bagetta et al. are the inhibitor of nNOS, 7-nitroindazole and according to Bagetta et al., 7-nitroindazole treats epilepsy and seizures.

The motivation to combine the teachings of Frederickson to the compounds of Bagetta et al. is that the compounds of Bagetta et al. are the inhibitor of nNOS, 7-nitroindazole and that such compounds, 7-nitroindazole, treat epilepsy and seizures.

Accordingly, absence the showing of unexpected results, it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy or seizures because the compounds of Suh et al. are chelatable zinc and according to Suh et al., chelated zinc treats epilepsy and seizures.

The motivation to combine the teachings of Frederickson to the compounds of Suh et al. is that the compounds of Suh et al. are chelatable zinc and that chelating zinc treats epilepsy and seizures.

It is noted that "It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose" and "It is obvious to combine two compositions taught by the prior art to be useful for the same purpose to form a third composition that is to be used for the very same purpose". *In re Kerkhoven*, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1 and 5-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 39, 41, 51, 56, and 60 of copending Application Frederickson et al. (10/929,924).

The claims of Frederickson et al. are directed to a liquid pharmaceutical preparation containing the estrogen ethinyl estradiol and the gestagen drospirenone for transdermal administration. The claims of Zurdo Schroeder et al. are obvious over the instant claims 1, 17, and 19 because the instant claims are directed to a pharmaceutical preparation of drospirenone and ethinyl estradiol for application to the skin.

This is a provisional double patenting rejection since the conflicting claims have not been patented.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

S. Wang